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Rhodium-Catalyzed Oxidative Coupling of Benzoic Acids with Terminal Alkynes: An Efficient Access to 3-Ylidenephthalides

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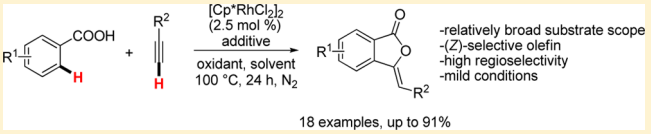
Supporting Information

ABSTRACT: Herein we disclose the first example of transition-metal-catalyzed oxidative coupling/annulation of simple benzoic acids with terminal alkynes via C−H activation. A range of aromatic carboxylic acids and terminal alkynes have been found to be viable substrates in this reaction, providing a simple and efficient method for the synthesis of diverse 3-ylidenephthalides with complete *Z* selectivity.



The phthalide structural motif is prevalent in many pharmaceuticals, natural products, and organic synthetic intermediates (Scheme 1).[1,2] In particular, 3-ylidenephthalides

Scheme 1. Examples of Biologically Active 3-Ylidenephthalides

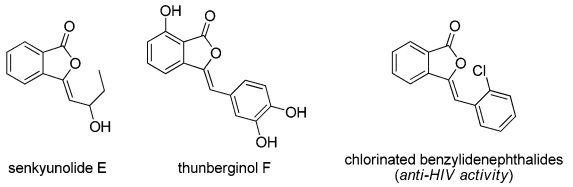
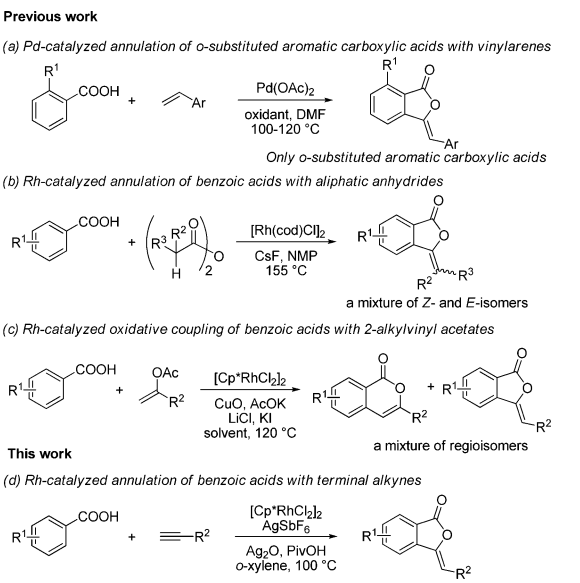


exhibit a broad spectrum of biological activities, such as anti-HIV, antidiabetic, antispasmodic, and antiallergic properties.[2a−e,3] Therefore, a number of methods have been developed to construct 3-ylidenephthalides,[4,5] including condensation of phthalic anhydrides with carboxylic acids,[5a,b] olefination of phthalic anhydrides,[5c] Baylis−Hillman reactions of 2-carboxybenzaldehyde,[5d] condensation of aromatic aldehydes with phthalides,[5e,f] transition-metal-catalyzed or -mediated carbonylation of ortho-substituted aryl ketones,[5g−i] and intramolecular cyclization of 2-(1-alkynyl)benzoic acids[5j,k] and alkenoic acids.[5l] From the viewpoint of atom and step economy, operational simplicity, and availability of substrates, transition-metal-catalyzed direct C−H functionalization is regarded as a more appealing strategy to streamline access to diverse complex molecules from simple substrates.[6] Miura and Lee realized the palladium-catalyzed oxidative annulation of ortho-substituted aromatic carboxylic acids with vinylarenes to synthesize (*Z*)-benzylidenephthalides (Scheme 2a).[7] Gooßen disclosed the rhodium-catalyzed sequential acylation/cyclization of benzoic acids with aliphatic anhydrides (Scheme 2b).[8] Wen reported the rhodium-catalyzed oxidative coupling of benzoic acids with 2-alkylvinyl acetates to give a mixture of isocoumarin and 3-alkylidenephthalide (Scheme 2c).[9] However, these protocols suffer from limitations such as narrow

Scheme 2. Synthesis of 3-Ylidenephthalides via Catalytic C−H Activation



substrate scope, high reaction temperature, moderate regioselectivity, and/or incomplete *Z*/*E* selectivity. Herein we disclose a rhodium-catalyzed oxidative annulation of benzoic acids with terminal alkynes to afford 3-ylidenephthalides in a completely *Z* selective manner (Scheme 2d). It is noteworthy that this is also the first example of transition-metal-catalyzed oxidative coupling/annulation of simple benzoic acids with terminal alkynes via C−H activation.

2-Methylbenzoic acid (**1a**) and ethynyltriisopropylsilane (**2**) were selected as the model substrates to optimize the reaction

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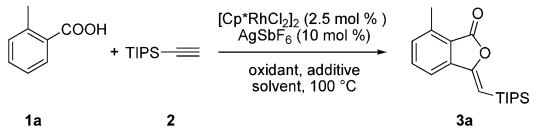
conditions (Table 1). In the presence of 2.5 mol % of $[Cp^*RhCl_2]_2$, 10 mol % of $AgSbF_6$, 2.0 equiv of Ag_2O, and 1.0 equiv of PivOH, a 55% yield of 3-ylidenephthalide **3a** was obtained in DCE, along with the generation of the alkyne dimer as a byproduct (entry 1). No desired product was detected in the absence of PivOH (entry 2). PivOCs was ineffective for this reaction (entry 3). The oxidant was next optimized. It was found that Ag_2CO_3 gave a slightly lower yield and AgOAc did not deliver any product (entries 4 and 5). Other oxidants, including $Cu(OAc)_2$, $K_2S_2O_8$, and BQ, were all unsuccessful in our tests (entries 6−8). The solvents were also examined. Very poor results were obtained in DMF and *t*-amylOH (entries 9 and 10). 1,4-Dioxane and toluene proved to be efficient, giving **3a** in 76% and 69% yields, respectively (entries 11 and 12). To our delight, the desired product was obtained in a 91% yield by employing a catalytic system comprising $[Cp^*RhCl_2]_2$ (2.5 mol %), Ag_2O (2.0 equiv), $AgSbF_6$ (10 mol %), and PivOH (1.0 equiv) in *o*-xylene at 100 °C for 24 h (entry 13). It is notable that only a trace amount of isocoumarin product was detected, indicating a high regioselectivity of this transformation. In addition, 2 equiv of Ag_2O was essential for a high reaction efficiency, presumably because the formation of silver(I) acetylide with excess alkyne consumed Ag_2O (entry 14). No reaction was detected in the absence of either $[Cp^*RhCl_2]_2$ or an oxidant (entries 15 and 16).

Table 1. Optimization of Reaction Conditions[a]



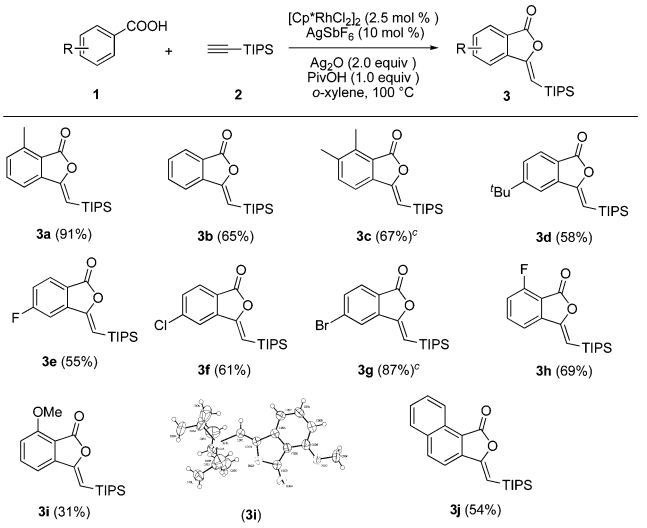
1a 2 3a

entry	oxidant	additive	solvent	yield (%)[b]
1	Ag_2O	PivOH	DCE	55
2	Ag_2O		DCE	n.d.
3	Ag_2O	PivOCs	DCE	n.d.
4	Ag_2CO_3	PivOH	DCE	49
5	AgOAc	PivOH	DCE	n.d.
6	$Cu(OAc)_2$	PivOH	DCE	n.d.
7	$K_2S_2O_8$	PivOH	DCE	n.d.
8	BQ	PivOH	DCE	n.d.
9	Ag_2O	PivOH	*t*-amylOH	trace
10	Ag_2O	PivOH	DMF	n.d.
11	Ag_2O	PivOH	1,4-dioxane	76
12	Ag_2O	PivOH	toluene	69
13	Ag_2O	PivOH	*o*-xylene	91
14[c]	Ag_2O	PivOH	*o*-xylene	41
15		PivOH	*o*-xylene	n.d.
16[d]	Ag_2O	PivOH	*o*-xylene	n.d.

[a]Reaction conditions: **1** (0.25 mmol), **2** (0.375 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (1.0 equiv), oxidant (2.0 equiv), and solvent (3.0 mL) at 100 °C for 24 h. Abbreviations: TIPS = triisopropylsilyl, DMF = dimethylformamide, *t*-amylOH = *tert*-amyl alcohol, n.d. = not detected. [b]Isolated yield. [c]Ag_2O (1.5 equiv) was used. [d]Without $[Cp^*RhCl_2]_2$.

With the optimized conditions in hand, we then examined the substrate scope of aromatic carboxylic acids (Table 2). Not only ortho-substituted but also benzoic acids that were unsubstituted and substituted at other positions were suitable substrates to deliver the desired products (**3a−d**). This result is distinctly different from that of previous reports,[7b] in which only ortho-substituted benzoic acids were effective. However,

Table 2. Scope of Benzoic Acids[a,b]

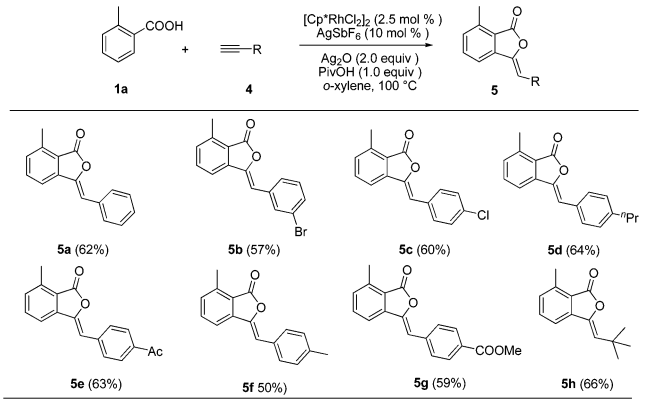


[a]Reaction conditions: **1** (0.25 mmol), **2** (0.375 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (0.25 mmol), Ag_2O (0.50 mmol), and *o*-xylene (3.0 mL) at 100 °C for 24 h. [b]Isolated yields. [c]DCE (3.0 mL) and Ag_2CO_3 (0.50 mmol) were used instead.

the ortho-unprotected benzoic acids typically exhibited less conversion efficiency, resulting in a great deal of unreacted substrates. Both electron-rich and -deficient benzoic acids were converted smoothly to the corresponding 3-ylidenephthalides (**3c−i**). However, a diminished yield was obtained when 2-methoxylbenzoic acid was used (**3i**). The configuration of **3i** was confirmed by single-crystal X-ray analysis. In addition, treatment of 1-naphthalenecarboxylic acid (**1j**) with ethynyltriisopropylsilane (**2**) under the standard conditions gave the corresponding product in 54% yield. It is notable that only *Z* isomers were observed in all cases.

The generality of alkynes was next investigated. As illustrated in Table 3, various aromatic alkynes **4** cyclized with 2-methylbenzoic acid (**1a**) to afford the corresponding 3-ylidenephthalides **5** in moderate to good yields (**5a−g**). Both electron-rich and -deficient phenylacetylenes were compatible with the reaction conditions. Some reactive functional groups, including acetyl, ester, and halogen, were tolerated under our

Table 3. Scope of Terminal Alkynes[a,b]



[a]Reaction conditions: **1a** (0.25 mmol), **4** (0.50 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (0.25 mmol), Ag_2O (0.50 mmol), and *o*-xylene (3.0 mL) at 100 °C for 30 h. [b]Isolated yields.

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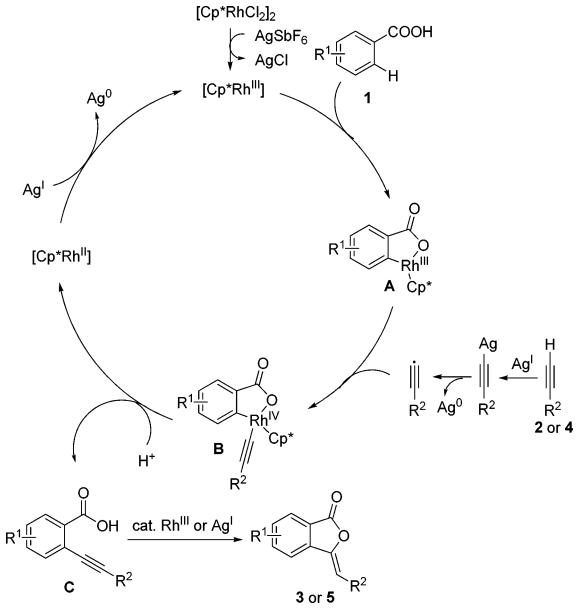
conditions. In addition to aryl alkynes, aliphatic alkynes could also be compatible in this transformation, delivering **5h** in a 66% yield. In contrast, only either 3-alkylidenephthalides or 3-arylidenephthalides could be accessed through the previously reported transition-metal-catalyzed C−H coupling of benzoic acids with unsaturated components.[6−8]

To probe the reaction mechanism, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was added. Only a trace amount of the desired product was detected in the presence of 0.5 equiv of TEMPO, thus implying that this reaction might involve a radical process.

While the mechanism of this reaction is still under investigation, a tentative mechanism is proposed on the basis of the above results and previous reports (Scheme 3).[5j,k,10]

Scheme 3. Proposed Mechanism



Initially, the coordination of the carboxylate oxygen atom of **1** to the electrophilic Rh(III) center and subsequent ortho C−H rhodation afford the rhodacycle **A**. A subsequent reaction with the in situ formed alkyne radical leads to the Rh(IV) complex **B**, which then undergoes reductive elimination to give the alkynylated product **C**.[11] A subsequent metal-catalyzed cyclization gives the desired product **3** or **5**. The released Rh(II) species is oxidized by silver(I) to regenerate the Rh(III) species to accomplish the catalytic cycle.

In summary, we have developed a facile and efficient route to 3-ylidenephthalides through a rhodium-catalyzed oxidative coupling/annulation of benzoic acids with terminal alkynes. This protocol features relatively broad substrate scope, mild conditions, operational simplicity, good regioselectivity, and excellent *Z* selectivity. Considering the wide applications of 3-ylidenephthalides in pharmaceuticals, our strategy would provide a great opportunity for rapid construction and evaluation of diverse 3-ylidenephthalides of potential pharmacological interest. Further investigation of the reaction mechanism is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00107.

Experimental procedures, characterization data, and NMR spectra (PDF)

X-ray crystallographic data for **3i** (CIF)

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Notes

The authors declare no competing financial interest.

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